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Patent Highlight

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New Substituted Cyanoindoline Derivatives as MAP3K14 Kinase Inhibitors for the Treatment of Cancer and Autoimmune Disorders

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Patent Application Title:	New Substituted Cyanoindoline Derivatives as MAP3K14 Kinase Inhibitors for the Treatment of Cancer and Autoimmune Disorders		
Patent/Patent Application Number:	WO2017125530 A1	**Publication date:**	July 27, 2017
Priority Application:	EP 16152416.0	**Priority date:**	January 22, 2016
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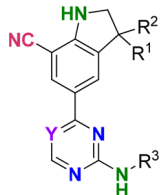
Disease Area:	Cancer, inflammatory, metabolic, and autoimmune disorders	**Biological Target:**	MAP3K14 kinase

Summary: The present invention relates to compounds useful for the treatment of diseases such as B-cell malignancies including leukemias, lymphomas, myeloma, inflammatory disorders, and so forth. The pharmaceutical agents inhibit the nuclear factor-kappa B (NF-κB)-inducing kinase (also known as MAP3K14 or NIK kinase). NF-κB is a transcription factor that regulates the expression of various genes involved in immune response, apoptosis, carcinogenesis, cell proliferation, and adhesion. NIK is a serine/threonine kinase, which regulates two NF-κB signaling pathways; the canonical and the noncanonical. The canonical pathway, also known as the "alternative" NF-κB pathway, mediates downstream signals of a subset of tumor necrosis factor (TNF) receptor family such as BR3/BAFF-R, CD40, and CD27. However, the noncanonical NF-κB pathway is involved in bone metabolism, B cell survival and maturation, lymphocyte recruitment, and so forth.

The noncanonical NF-κB pathway is selectively activated by ligands such as CD40, B-cell activating factor (BAFF), TNF-related weak inducer of apoptosis (TWEAK), and lymphotoxin β receptor ligands. As a result, NIK expression is tightly regulated, and under nonstimulated conditions, the NIK protein levels are very low. However, when stimulated by ligands, the activated receptors now compete for TNF receptor associated factors (TRAFs), which dissociates the TRAF-NIK complexes and leads to increased levels of NIK, which is seen in many disease processes. There are reports that have shown that blocking the NF-κB signaling pathway in cancer cell lines causes cells to stop proliferating, become more sensitive to anticancer therapies, and eventually die. Furthermore, NIK is dysregulated in multiple myeloma because of diverse genetic abnormalities. In addition, NIK has been shown to exacerbate disease conditions in chronic obstructive pulmonary disease (COPD), diabetes, rheumatoid arthritis (RA), and so forth. Thus, the present invention is directed to a series of pharmaceutical compounds such as Formula (I) for the prevention or treatment of diseases such as cancer, obesity, diabetes, and autoimmune disorders.

Important Compound Classes:



Formula (I)

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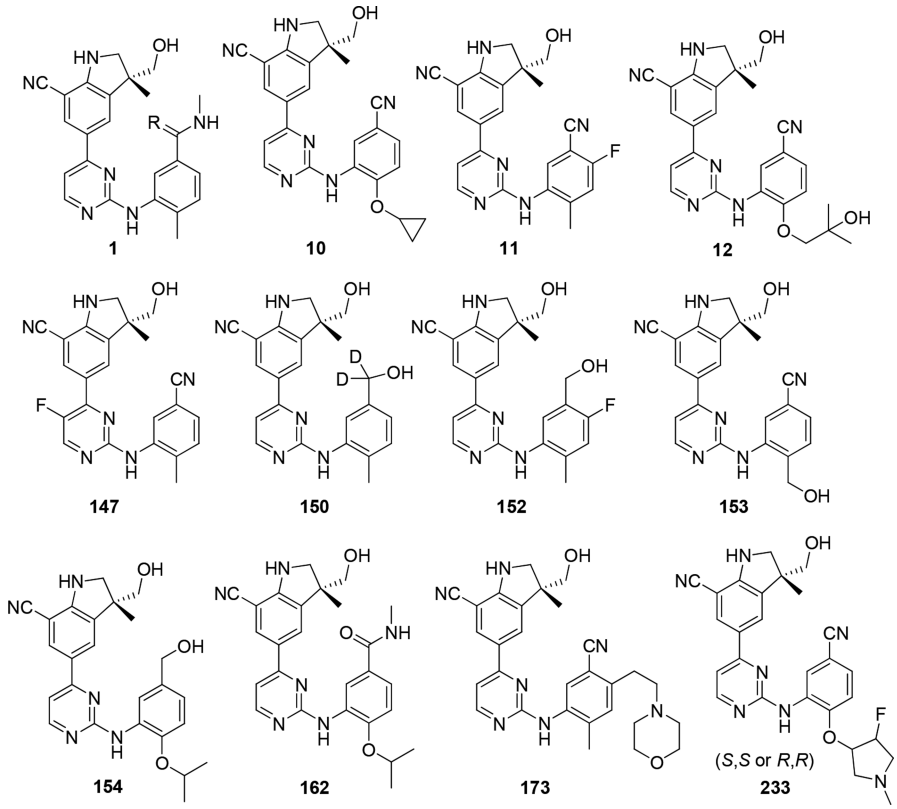
Key Structures: The inventors described synthetic procedures and listed structures of 240 compounds of Formula (I) including the following representative examples:



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2. Limerick, G.; Tang, X.; Lee, W. S.; Mohamed, A.; Al-Aamiri, A.; Wadsworth, W. G. *Neuroscience* **2017**, 1−81.

3. Rapino, F.; Abhari, B. A.; Jung, M.; Fulda, S. *Cell Death Dis.* **2015**, *6*, 1692.

Biological Assay: There were three biological assays used in this patent:

(1) The NIK/MAP3K14 autophosphorylation activity was measured using the Alpha Screen (*α*screen) format (PerkinElmer). The compounds were tested for inhibition of the autophosphorylation of recombinant human NF-kappaB-inducing kinase (NIK/MAP3K14) activity. Assays were carried out in 384-well Alphaplates (PerkinElmer).

(2) Compounds of interest were tested in P-IKK*α* levels of L363 (NIK translocated multiple myeloma) cells. The human L363 cells (ATCC) were cultured in RPMI 1640 medium, which was supplemented with GlutaMax and 10% fetal calf serum (PAA).

(3) Determination of antiproliferative activity on JJN-3 (NIK translocated) and KMS12-BM (NIK WT) multiple myeloma cells. The cell viability was assessed using CellTiter-Gluo cell viability assay kit (Promega). The human JJN-3 and KMS12-BM cells (DSMZ) were cultured in RPMI 1640 medium and supplemented with 2 mM L-glutamine and 10% fetal calf serum (PAA). Luminescence was measured on a HTS Topcount (PerkinElmer).

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Biological Data: The biological data obtained from testing the above representative compounds of Formula (I) are listed in the following table:

Entry	Compound	Auto-phosphorylation inhibition of NIK [IC_{50} (nM)]	Inhibition of pIKKα_L-363 [IC_{50} (nM)]	KMS-12 Proliferation Inhibition [IC_{50} (nM)]	JJN-3 Proliferation Inhibition [IC_{50} (nM)]
1	**1**	1.8	2.2	5188	85
2	**10**	7.4	11.5	1227	67
3	**11**	1.8	6.0	>10000	617
4	**12**	4.1	25.7	4898	138
5	**147**	3.9	1.2	>10000	302
6	**150**	0.8	2.2	>10000	91
7	**152**	2.3	7.8	>10000	272
8	**153**	1.3	6.3	>10000	240
9	**154**	1.4	6.6	>10000	141
10	**162**	5.5	19.5	>10000	288
11	**173**	1.8	1.3	>10000	29
12	**233**	4.6	21.4	>10000	741

Claims: 33 Total claims

27 Composition of matter claims

6 Method of use claims

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Notes

The author declares no competing financial interest.

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